Neonatal Foal 2:

Sepsis, Neonatal Encephalopathy
(Neonatal Maladjustment Syndrome)

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Outcome

- List clinical signs and understand the pathophysiology of Sepsis and Neonatal Encephalopathy
- Select diagnostic and treatment options for Sepsis and Neonatal Encephalopathy

You will only be tested on materials covered in lecture, extra material in notes is for your information only

Sepsis and Septic Shock

- ***Sepsis***: Life-threatening organ dysfunction caused by dysregulated host response to infection

- ***Foal Sepsis***: A life-threatening condition involving proven or suspected infection, with systemic manifestations of infection (2024).

- ***Septic Shock***: Subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality

- ***Bacteremia***: The presence of bacteria within the bloodstream, confirmed by culture.

- Equine Sepsis: Mortality 50%

Pathophysiology

- **Systemic inflammatory response syndrome - SIRS** (manifest as fever/hypothermia, tachycardia, tachypnea, leukopenia/leukocytosis)

- **Sepsis** – SIRS + bacteremia

- **Septic Shock** – Severe sepsis with refractory hypotension

- **Multiple organ dysfunction syndrome (MODS)** [pneumonia, enterocolitis, omphalophlebitis, septic arthritis]
  - The hypothalamic-pituitary-adrenal axis dysfunction may increase mortality in septic foals

- **Onset:** first 2 weeks of life

Pathogenesis

- Foals host defenses are overwhelmed
  - May occur *in utero* or after birth
  - Number and virulence of the infecting organism matters
  - Host immune status—**Failure of Passive Transfer**, concurrent disease all increase risk
  - **Access**: GI tract, Respiratory tract, Umbilicus or a site of infection

- Gram negative enteric organisms most prevalent
  - Opportunistic bacteria (non virulent ***E coli*** for example)
  - Pathogenic bacteria (*Salmonella spp* for example)

Risk Factors

- Lack of good colostrum
  - Failure of Passive Transfer, poor local defenses, delayed gut closure

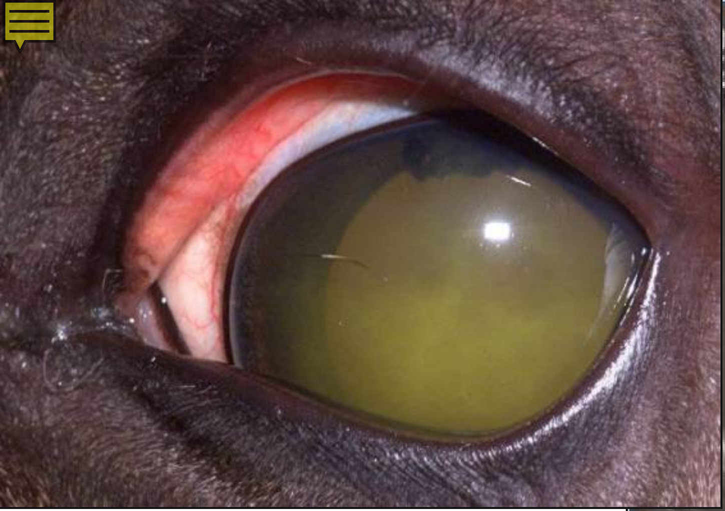
- Illness-especially infections- omphalophlebitis, enteritis, pneumonia, etc

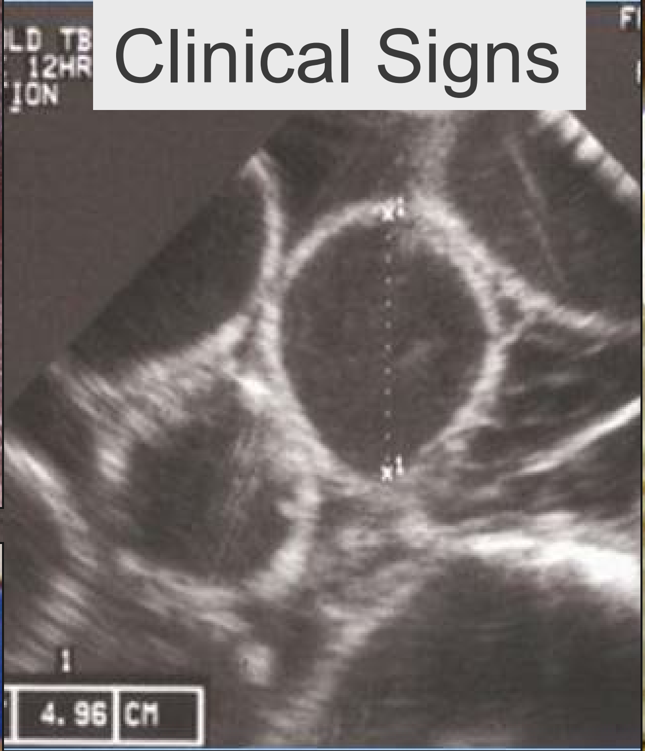
- Neonatal maladjustment syndrome

- Maternal illness

- Other complication-dystocia, hypoxia, placentitis, twins, prematurity, adverse environmental condition, etc

Clinical Signs

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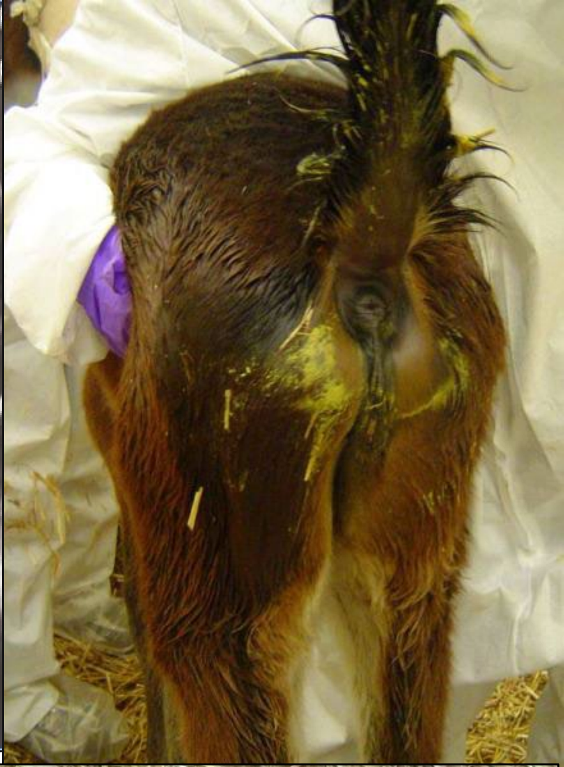
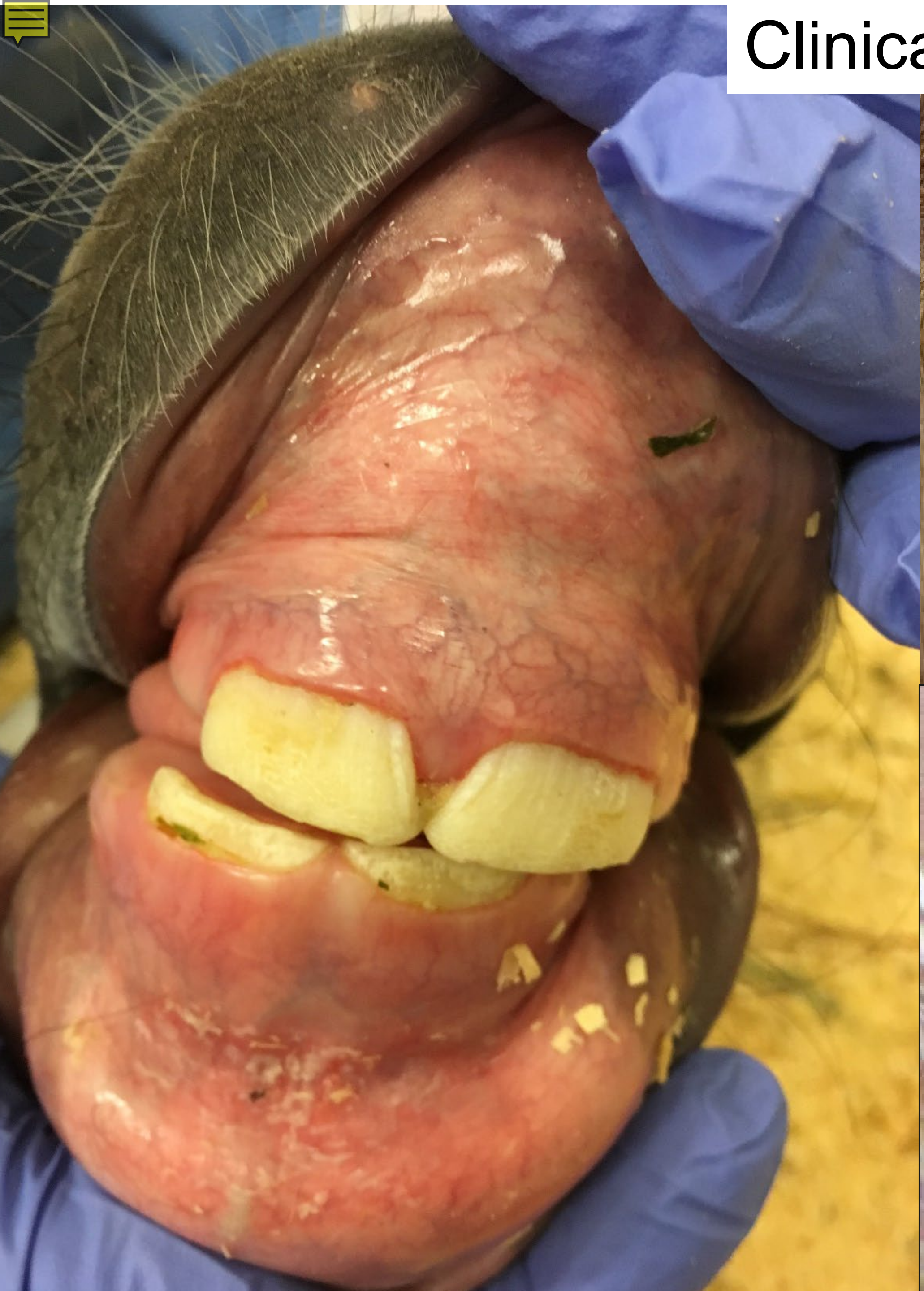
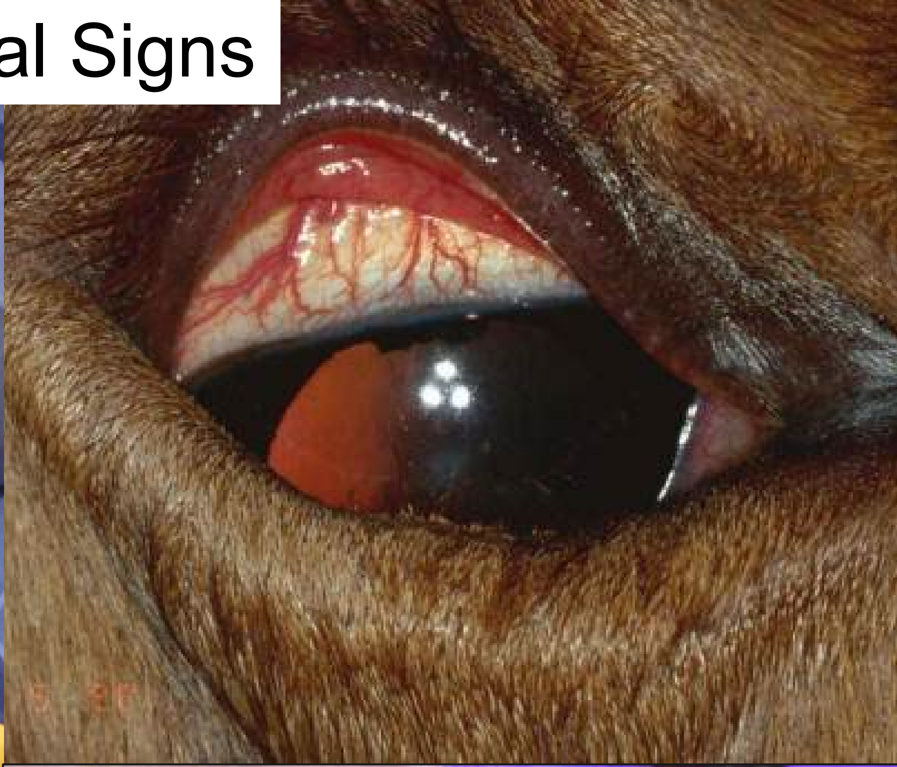
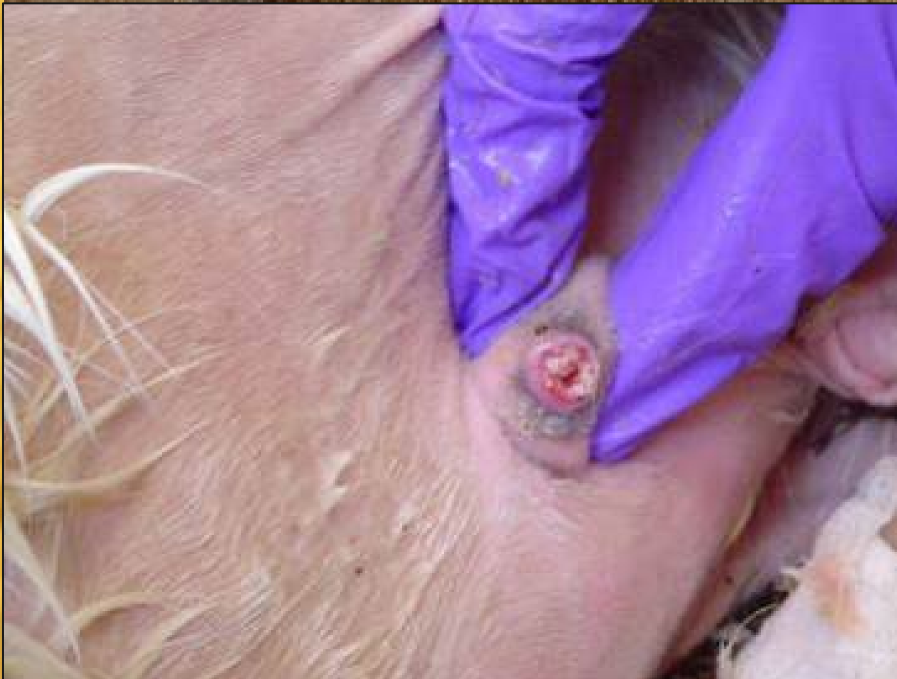


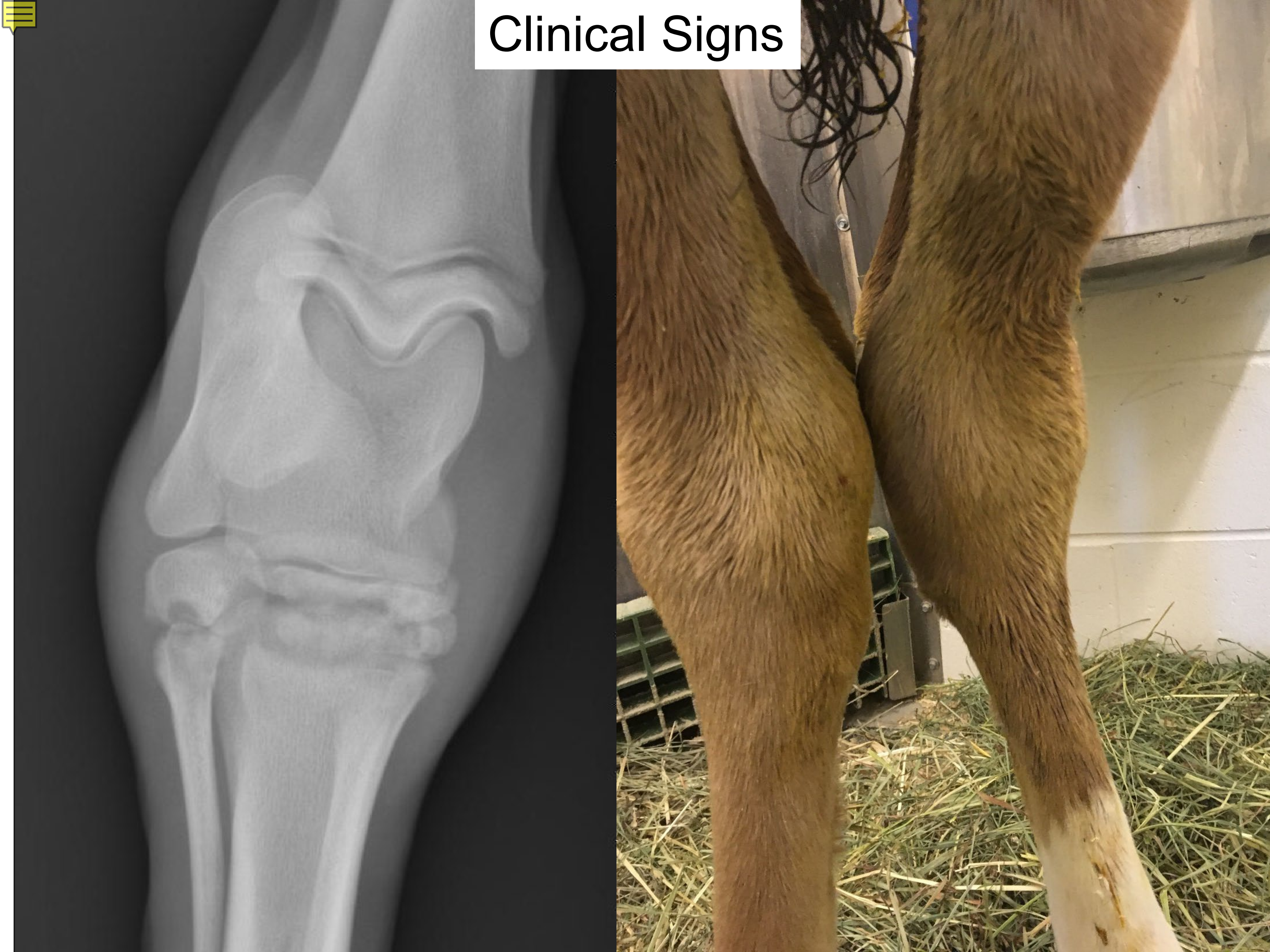
Clinical Signs



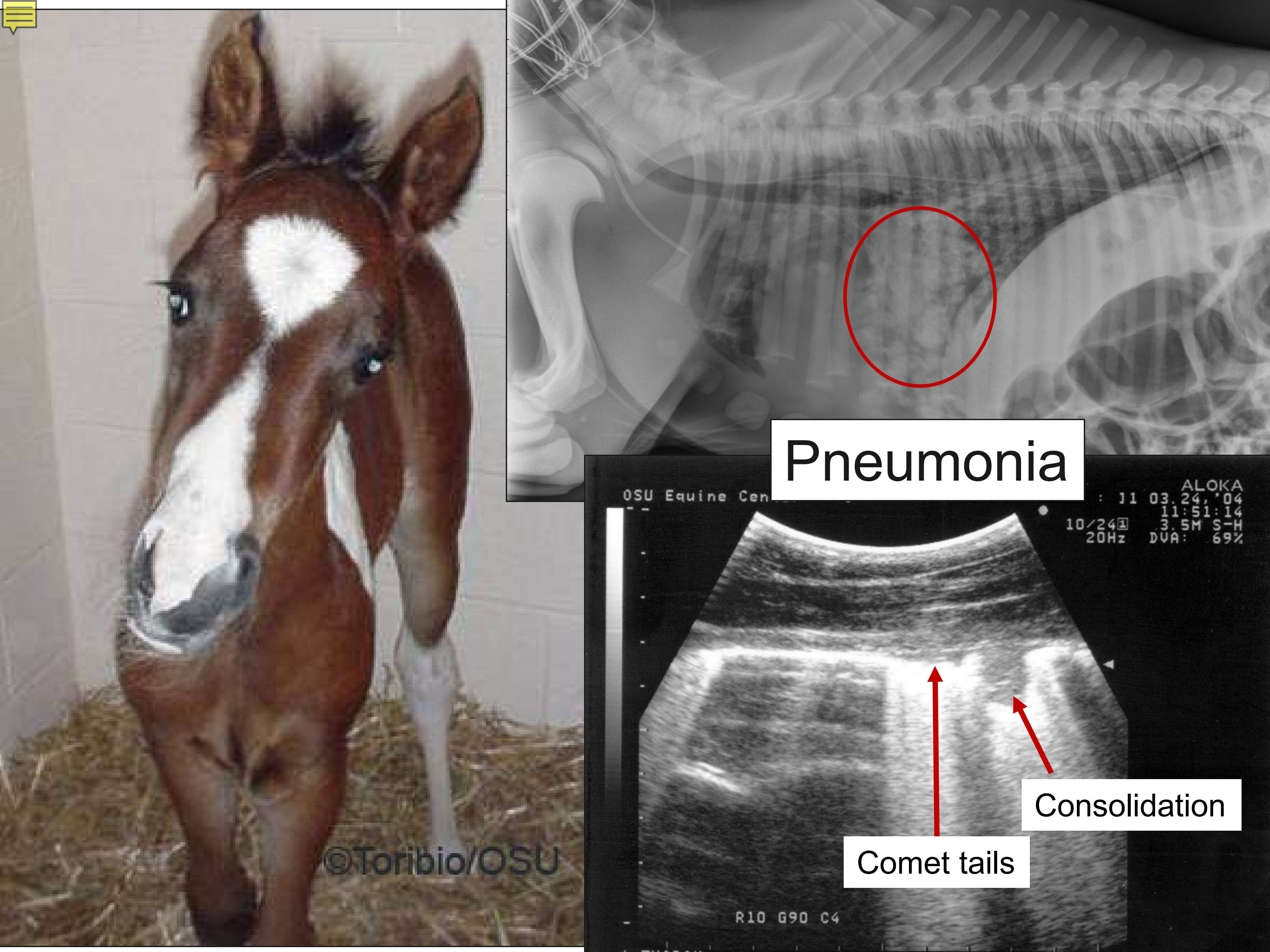




Clinical Signs



Pneumonia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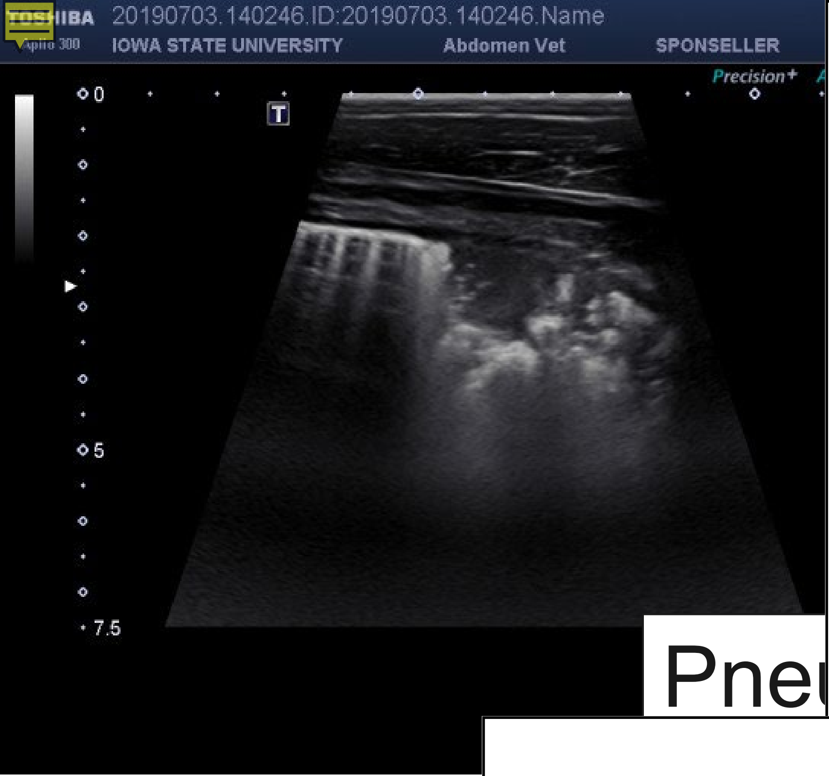
Comet tails

Consolidation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Pneu

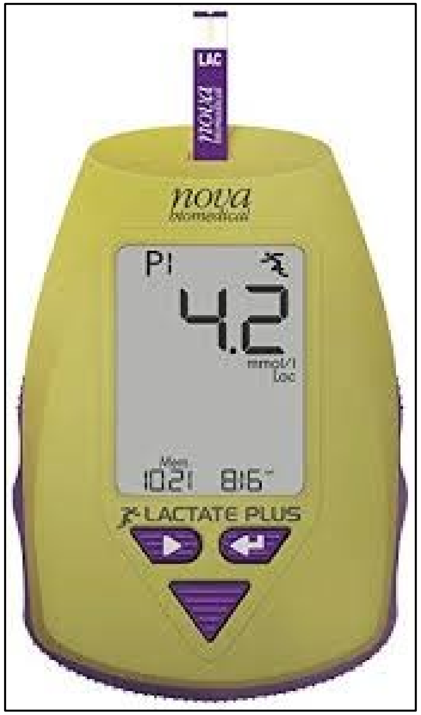
Pleural fluid

Fibrin

Sepsis and Septic Shock

Clinicopathologic Abnormalities

- ✓ Biochemistry Profile
  - ✓ Hypoglycemia
  - ✓ Hyperlactatemia
  - ✓ Electrolyte Derangements
    - ✓ Hyponatremia
    - ✓ Hypochlormemia
  - ✓ Azotemia
    - ✓ Placental insufficiency
  - ✓ Acidosis
  - ✓ High liver enzymes
  - ✓ Reflects organ dysfunction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nova biomedical
PI
4.2
mmol/l
Lac
Mem
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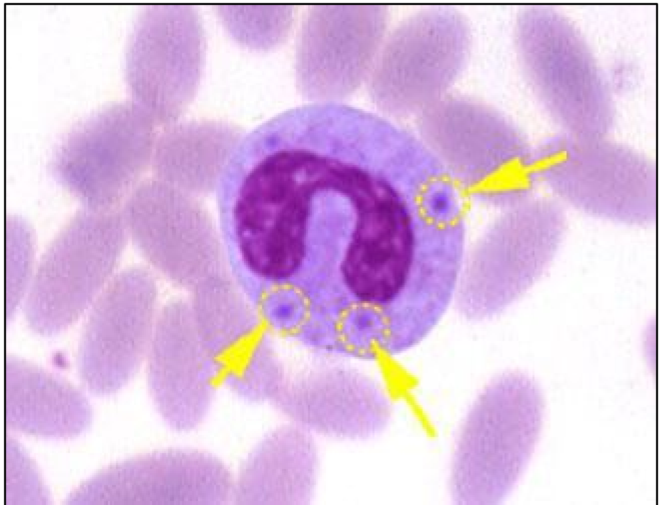
LACTATE PLUS

Sepsis and Septic Shock

Clinicopathologic Abnormalities

- ✓ **CBC**
  - ✓ Leukopenia
  - ✓ Neutropenia
    - ✓ Toxic morphologic changes
  - ✓ Increased Bands
  - ✓ Increased Fibrinogen
  - ✓ Increased Serum Amyloid A
  - ✓ Thrombocytopenia



Sepsis and Septic Shock

- **Diagnosis**
  - History
  - Clinical Signs
  - Clinicopathological Data
  - Positive Bacterial Culture of Blood Sample – **the gold standard**
    - 24-48h
    - 40-50% of septic foals → negative blood culture
      - Low sensitivity

Hackett ES, Lunn DP, Ferris RA, Horohov DW, Lappin MR, McCue PM, 2015.
Detection of bacteraemia and host response in healthy neonatal foals.

Sepsis Score

Brewer BD1, Koterba AM. 1988. **Development of a scoring system for the early diagnosis of equine neonatal sepsis**

- **Sepsis Score** – scoring protocol developed for foals to evaluate for likelihood that sepsis is present in foal without performing a blood culture

- The sepsis score is not completely accurate
    - Sensitivity 50-60%

oal's Hospital Name ______________________

Information collected:		4	3	2	1	0	This case
I. CBC 1. Neutrophil count ($\times 10^9$/L)	Record exact #		<2.0	2.0-4.0 or >12.0	8.0-12.0	Normal	
2. Band neutrophil count ($\times 10^9$/L)			>0.2	0.05-0.20		<0.05	
3. Doehle bodies, toxic, granulation, or vacuolation in neutrophils		Marked	Moderate	Slight		None	
4. Fibrinogen (g/L)				>6.0	4.01-6.0	≤4.0	
II. Other laboratory data 1. Blood glucose (mmol/L)				<2.78	2.78-4.44	>4.44	
2. IgG quick test (g/L)		<2.0	2.0-4.0	4.01-8.0		>8.0	
III. Clinical Examination 1. Petechiation or scleral injection not secondary to eye disease or trauma			Marked	Moderate	Mild	None	
2. Fever (°C)				>38.9	<37.8	Normal	
3. Hyponatremia, coma, depression convulsions				Marked	Mild	Normal	
4. Anterior uveitis, diarrhea, respiratory distress, swollen joints, open wounds			Yes			No	
IV. Historical data 1. Placentitis, vulvar discharge prior to delivery, dystocia, long transport of mare, mare sick, foal induced, gastrointestinal age >365 d			Yes			No	
2. Prematurity			<300 days	300-310	311-330	>330	

TOTAL ☐

Pathogens

- Gram negative
  - **Escherichia coli**
  - Klebsiella spp
  - Enterobacter spp
  - Salmonella spp
  - Actinobacillus spp
  - Proteus spp
  - Pseudomonas spp
- Gram positive
  - Streptococcus
  - Enterococcus
  - Staphylococcus

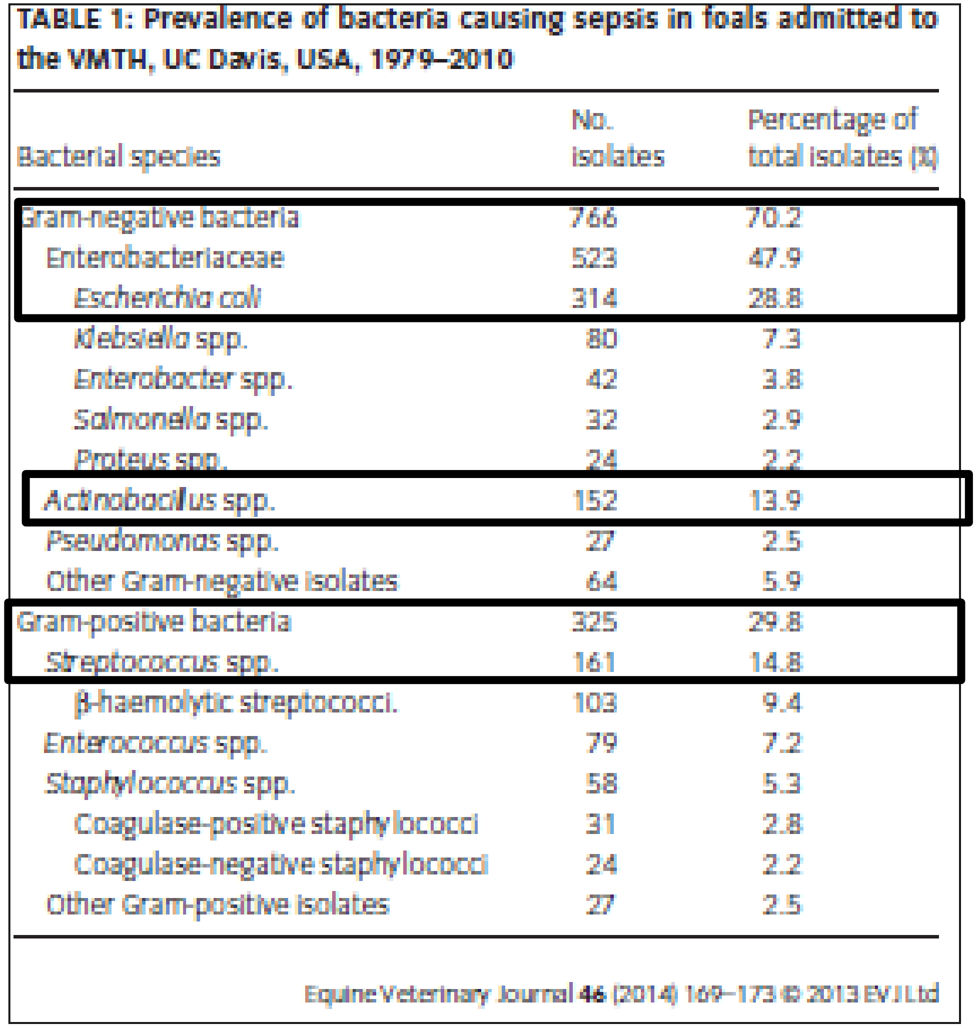


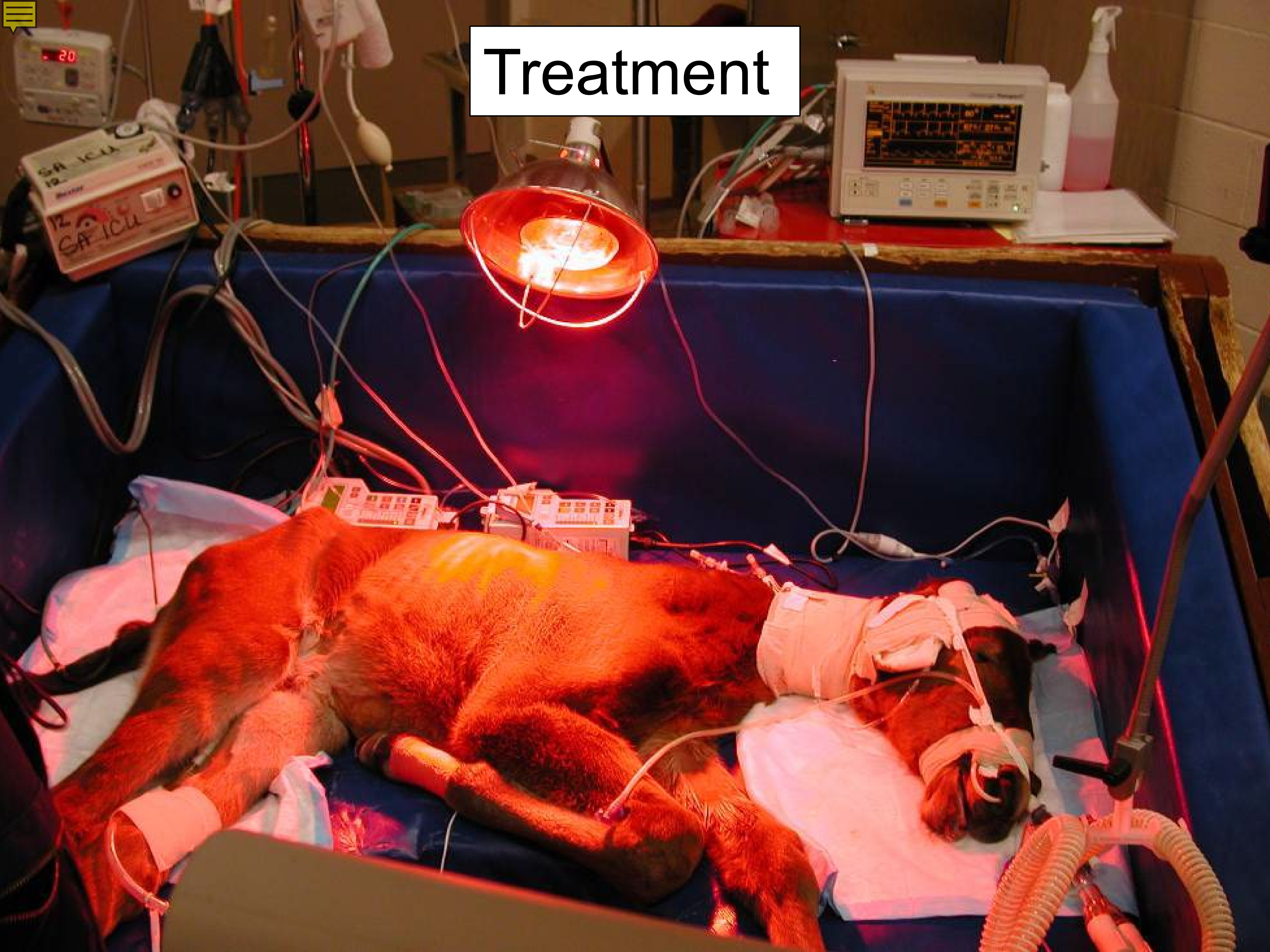
TABLE 1: Prevalence of bacteria causing sepsis in foals admitted to the VMTH, UC Davis, USA, 1979–2010

Bacterial species	No. isolates	Percentage of total isolates (%)
Gram-negative bacteria	766	70.2
Enterobacteriaceae	523	47.9
Escherichia coli	314	28.8
Klebsiella spp.	80	7.3
Enterobacter spp.	42	3.8
Salmonella spp.	32	2.9
Proteus spp.	24	2.2
Actinobacillus spp.	152	13.9
Pseudomonas spp.	27	2.5
Other Gram-negative isolates	64	5.9
Gram-positive bacteria	325	29.8
Streptococcus spp.	161	14.8
β-haemolytic streptococci.	103	9.4
Enterococcus spp.	79	7.2
Staphylococcus spp.	58	5.3
Coagulase-positive staphylococci	31	2.8
Coagulase-negative staphylococci	24	2.2
Other Gram-positive isolates	27	2.5

Equine Veterinary Journal **46** (2014) 169–173 © 2013 EVJ Ltd

M. THEELEN, W. WILSON, J. EDMAN, K. MAGDESIAN and P. KASS, 2014, **Temporal trends in prevalence of bacteria isolated from foals with sepsis: 1979-2010.**

Treatment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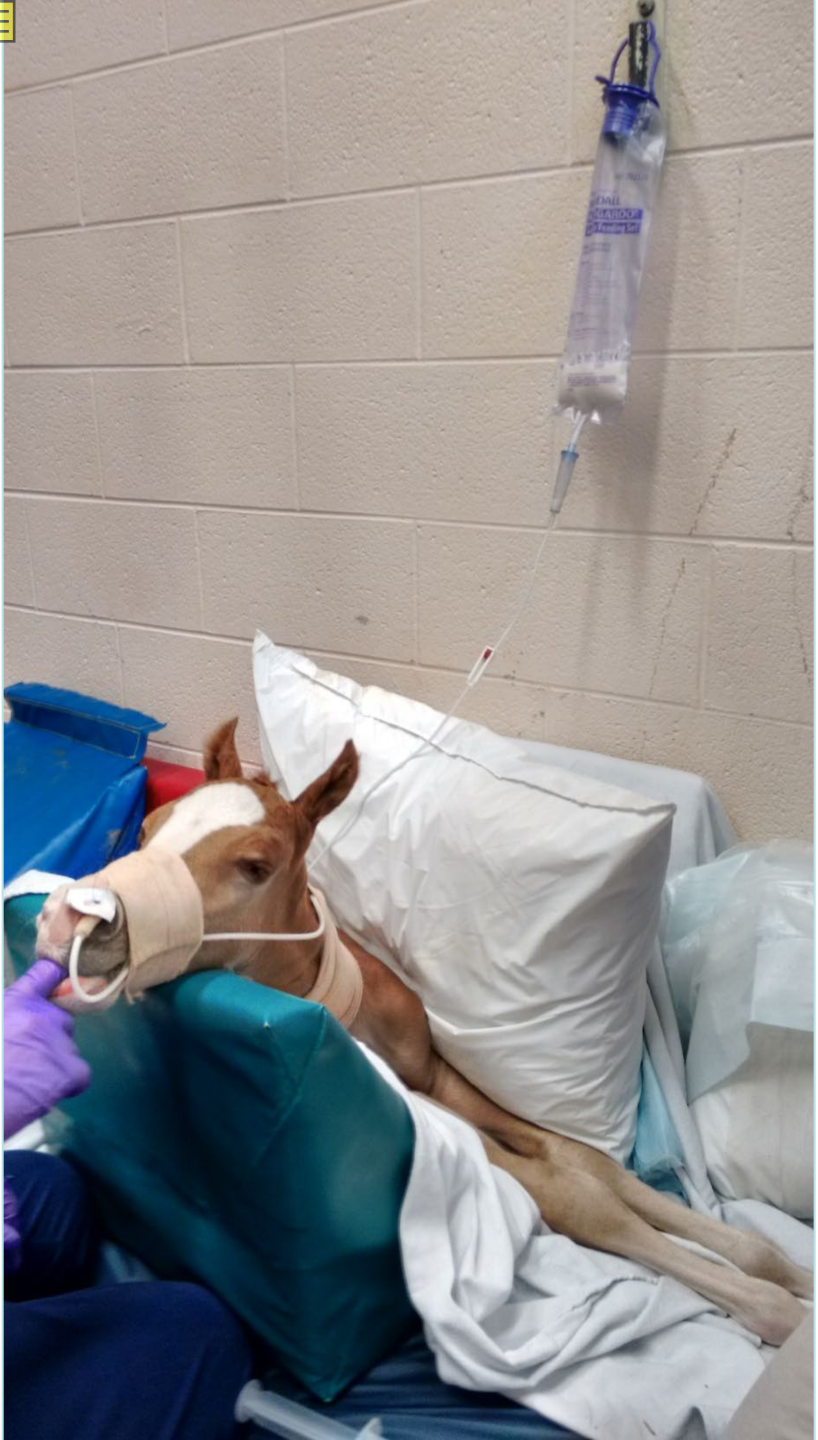
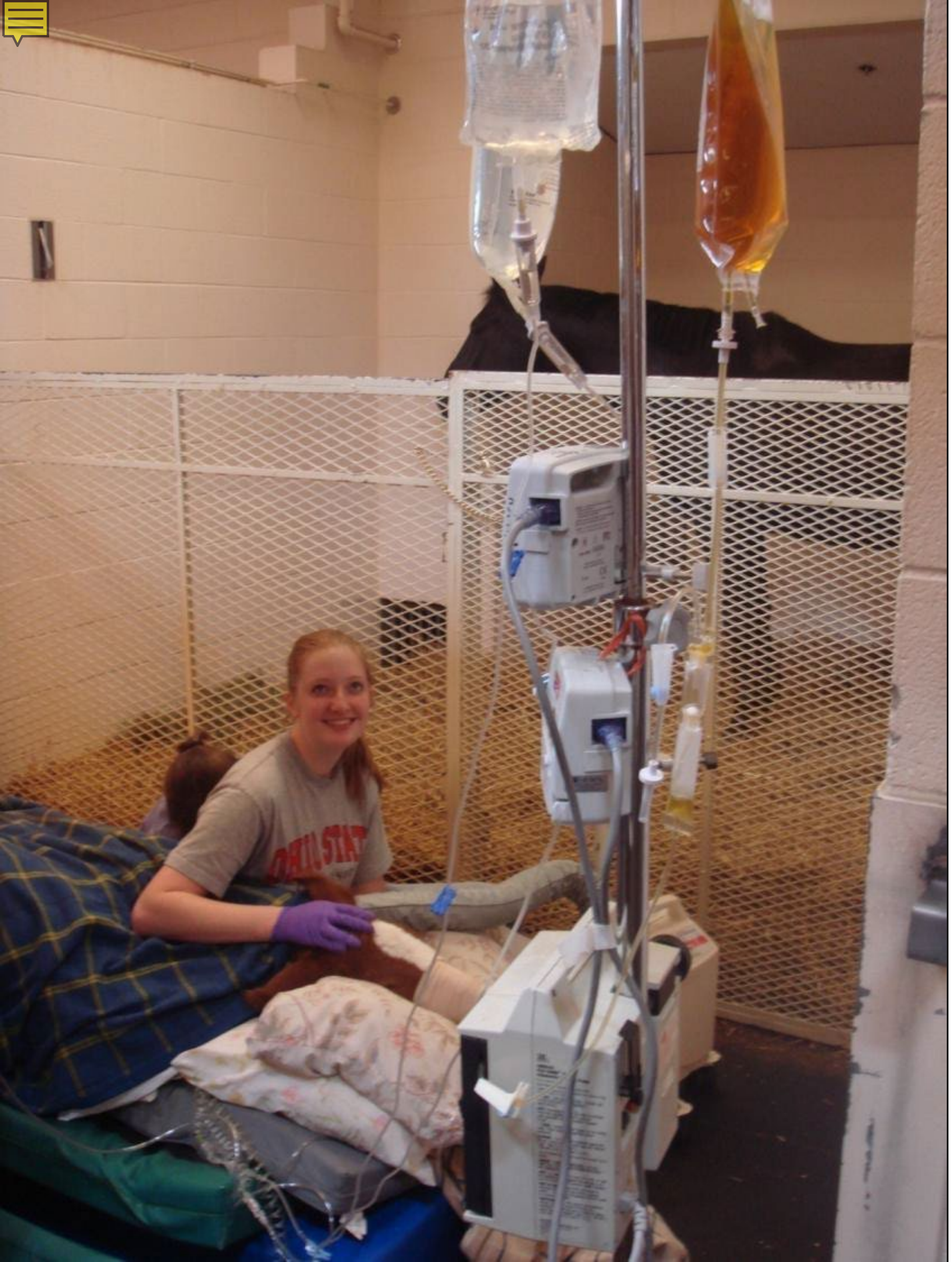
SA ICU
12
SA ICU



- **< 12h – Colostrum**



HiGamm-EquiTM
For Veterinary Use Only
500 ml
Normal Plasma,Equine Origin
IgG ≥ 2500 mg/dl

for Intravenous use as an aid in the supportive treatment of hypoproteinemia or the failure of passive transfer of maternal antibodies in the foal. The diagnosis of failure of passive transfer of antibodies should be established from a blood sample taken at least 18 hours after birth.

Each single dose bag contains high gamma globulin equine plasma with sodium citrate as an anticoagulant derived from healthy horses with no A or Q r.b.c. factors and no serum r.b.c. antibodies. All donor horses are negative for EIA and EVA. There is no preservative added.

Directions for use: KEEP FROZEN UNTIL USE. Thaw slowly not exceeding 120°F. Administer by slow filtered intravenous infusion. Discard the unused portion. In case of a reaction, marked most often by tenesmus and hyperventilation, slow the speed of administration. If this does not abate the signs, stop administration until signs abate, then continue administration at a slower rate. If signs persist, suspend administration - treat with antihistamines and anti-inflammatory agents. HiGamm-EquiTM administration may be attempted again after treatment to relieve adverse response has been successful.

Caution — The possibility of transmission of viral disease is possible with the administration of any blood product. This is a rare occurrence.

Serial No: HJ09079
Expiration Date: SEP. 0 7 1992
Vet Lic. No. 316
LAKE IMMUNOGENICS, INC.
Ontario, New York 14519

>12 h – Plasma IV

الخالدية
AL KHALEDIAH
Plasma
Equine Origin
Batch Number: 0210080504
Expiry: 02/2010
FOR AKF USE ONLY

β-lactam antibiotics

- Penicillin
  - Penicillin K
  - Ampicilin Na
- Cephalosporin
  - Ceftiofur Na
  - Cefpodoxime – **P.O**.

NDC 0049-0530-28
Buffered
Pfizerpen®
(penicillin G potassium)
For Injection
TWENTY MILLION UNITS 20
FOR INTRAVENOUS INFUSION ONLY
Pfizer Roerig
NDC 0015-7404-20
NSN 6505-00-993-3518
EQUIVALENT TO
1 gram AMPICILLIN
Ampicillin for Injection, USP
For IM or IV Use
Rx only

ROCHE LABORATORIES INC. Nutley, New Jersey 07110
Single Use Vial
1 gram
ROCEPHIN®
(ceftriaxone sodium)
For I.M. or I.V. Use
NDC 0039-0019-01
Claforan® Sterile
cefotaxime for injection, USP
2 g
FOR IM/IV ADMINISTRATION
One 2g Vial
Aventis
3013
DEC-2004
NDC 0173-0379-34
Fortaz®
(ceftazidime for injection)
2 g
Rx only
Equivalent to 2 g of ceftazidime. For IV use.
Naxcel®
4 grams
Sterile Powder
ceftiofur sodium sterile powder
LOT 2122NX
EXP 12/04
Pharmacia & Upjohn

- **Aminoglycosides**
  - **Amikacin**
  - Gentamicin
- Metronidazole: anaerobic bacteria

- **Amikacin + ampicillin or penicillin usually the best choice**
- Ceftiofur or gentamicin/penicillin second best choices

- Polymixin B – binds endotoxin

NDC 0677-0816-01
URL
METRONIDAZOLE TABLETS, USP
500 mg
100 TABLETS
℞ only
MANUFACTURED FOR UNITED RESEARCH LABORATORIES, INC. PHILADELPHIA, PA 19124 USA

NDC 0856-2332-20
Amiglyde-V®
AMIKACIN SULFATE
FORT DODGE
Veterinary Solution
Equivalent to 250 mg amikacin per mL
12 gram – 48 mL
NADA 127-892, Approved by FDA

NDC 50989-193-12
GentaVed™ 100
(Gentamicin Sulfate Solution)
100 mg/mL Gentamicin
Sterile Multiple Dose Vial
NET CONTENTS: 100 mL
VEDCO
ANADA 200-137, Approved by FDA

POLYMYXIN B
FOR INJECTION
Sterile
500,000 UNITS
Rx ONLY.

Fluid Therapy

- Shock-resuscitation
  - Isotonic crystalloid fluids-boluses
  - Hypertonic saline for resuscitation

- Can use plasma as a protein replacement or a colloidal fluid
- Correct hypoglycemia and electrolyte/acid base abnormalities
- Volume:
  - Resuscitation generally 1-2 L of isotonic fluids
  - Correct dehydration based on % body weight

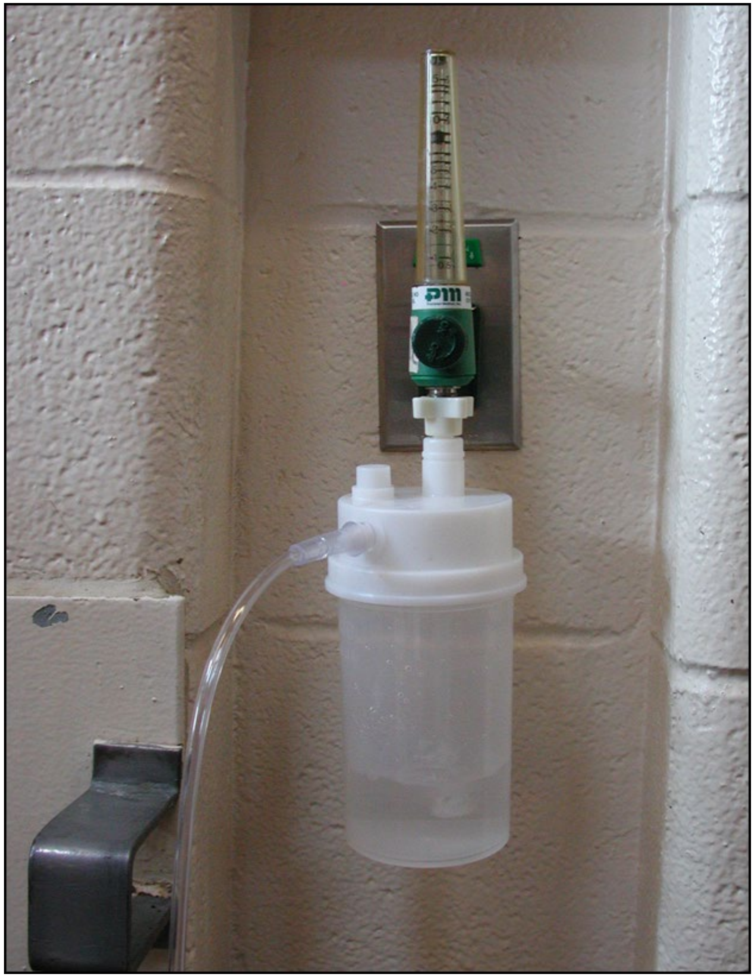
    Maintenance 80-100 ml/kg/day
- Type of Fluids

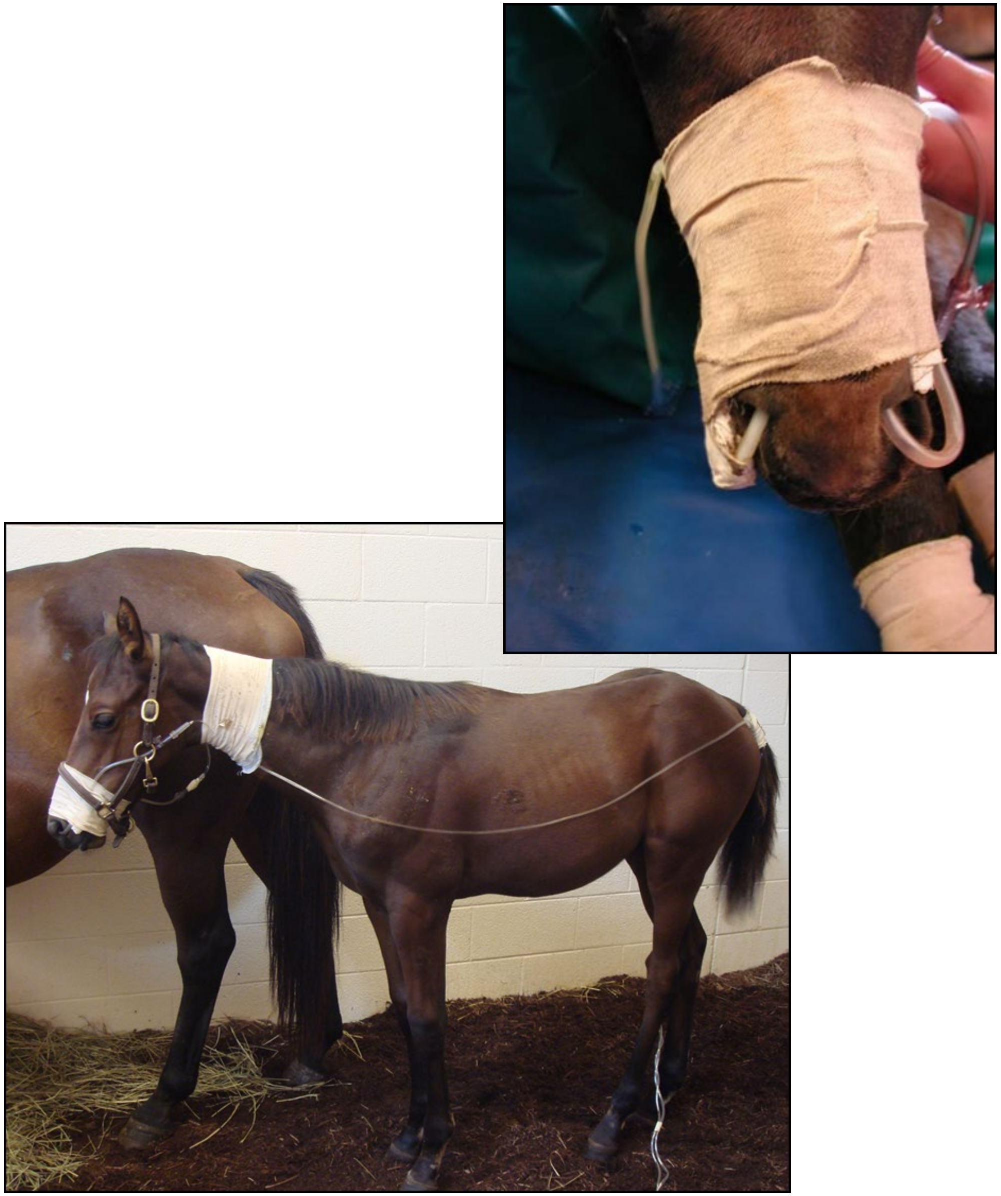
Plasmalyte A or M (contains 5% dextrose) is a good choice

Plasma-Lyte
148 Injection
(Multiple Electrolytes
Injection Type 1 USP)
1000 mL

Monitor urine output, urine specific gravity, weight, PCV/TP, electrolytes, pH, glucose, lactate

Oxygen





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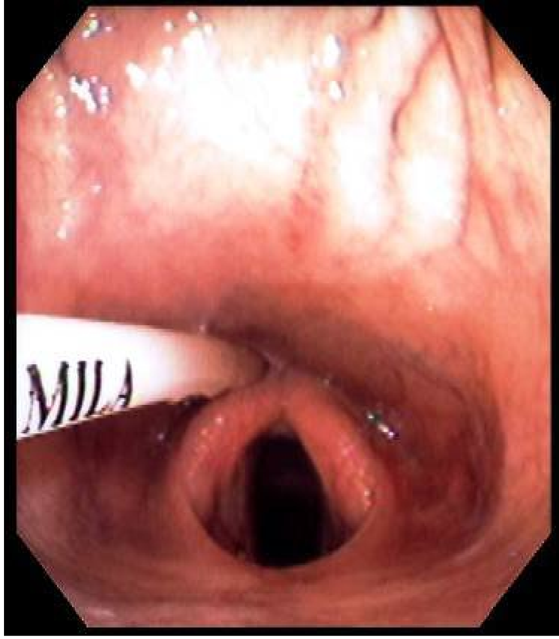
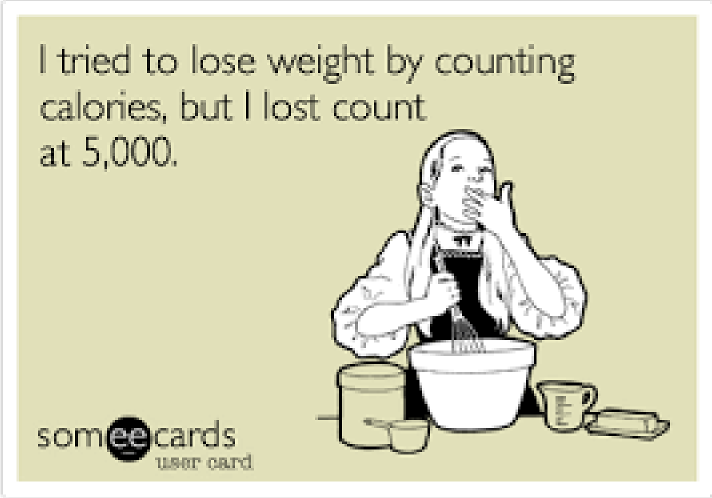


Energy

5% Dextrose
Injection USP
1000 mL
Baxter

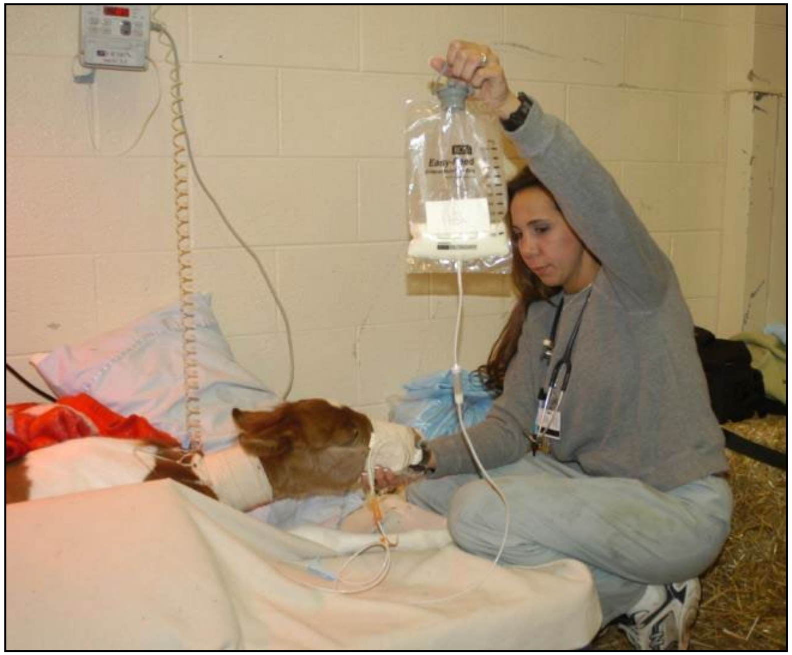


I tried to lose weight by counting calories, but I lost count at 5,000.

someecards
user card

Feeding the Neonatal Foal

- **Calculate amount to be fed**
  - Start with 5% foal's body weight (move up to 20-25% BW over several days)
    - 50kg x 5% = 2.5 liters = 2500 mLs/day = 200 mLs every 2 hours
  - Mares milk is best or mares milk replacer
- Warm milk to room temp and place in feeding bag
- Put foal in sternal recumbency
- Check for reflux
- Connect milk bag to NG tube
- Gravity flow milk through NG tube
- Flush NG tube with H2O
- Monitor for ileus-reflux or colic
- Total or partial **parenteral nutrition** if oral feeding not tolerated



Anti-inflammatory

NDC 0856-4396-02
Ketofen®
KETOPROFEN
FORT DODGE
100 mg/mL
Sterile Solution
100 mL
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA 140-269, Approved by FDA

- **NSAIDs**
  - Flunixin meglumine(0.25 –0.5 mg/kg IV SID)
  - Contraindicated with renal disease, dehydration, enteritis
  - Monitor for nephrotoxicity or GI ulceration
- **Steroids**
  - no evidence of benefit EXCEPT possibly in **relative adrenal insufficiency**, steroid replacement (hydrocortisone) may have a benefit

NDC 0856-0851-10
Flunixamine™
FLUNIXIN MEGLUMINE INJECTION
FORT DODGE
50 mg/mL
100 mL

Other treatment

- Prevent gastric ulcers:
  - Omeprazole PO
  - Sucralfate

- Pressors if needed - dobutamine by CRI are most effective

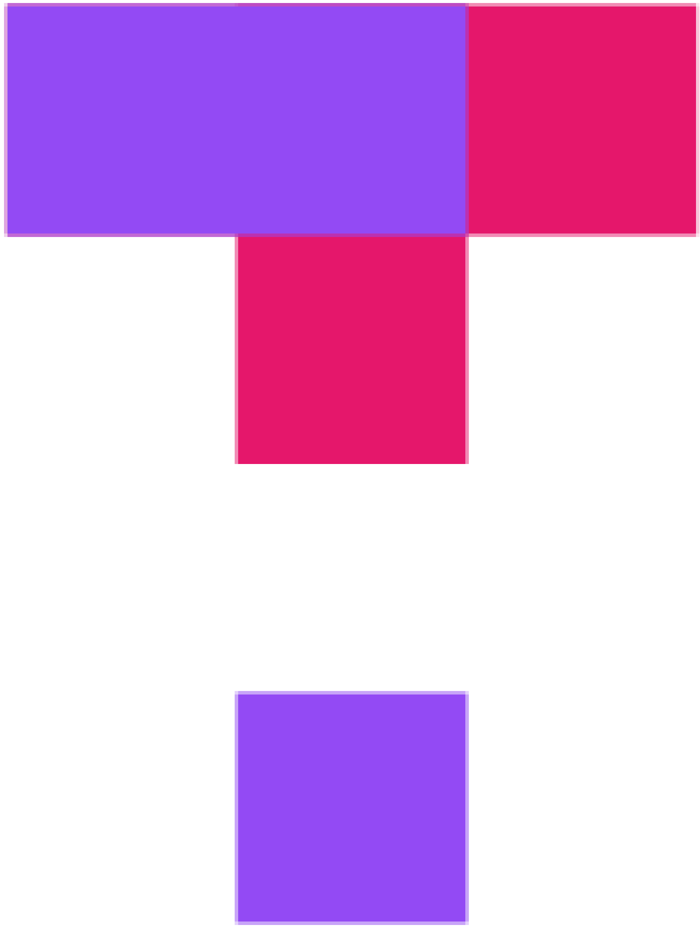
Sepsis

Sepsis - Prognosis

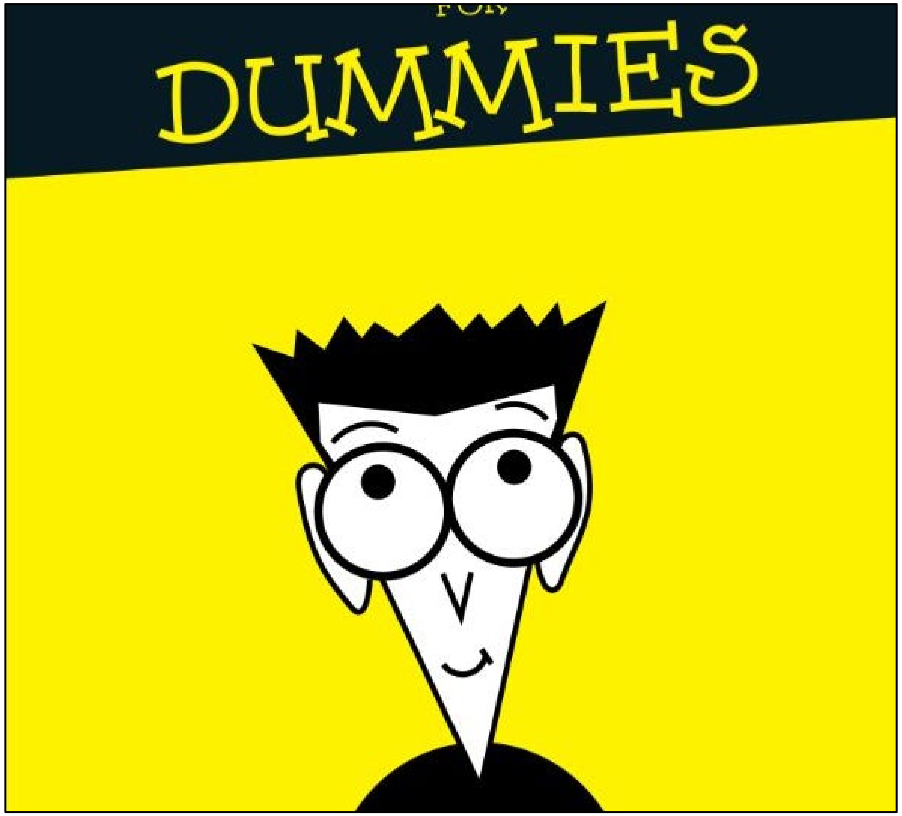
- Some foals just need a boost in calories, some milk and broad-spectrum antibiotics
- Some foals succumb to sepsis regardless of what you do

- **Variables to help predict prognosis**:
  - ✓ Blood lactate
  - ✓ Clinicopathologic changes
- Hypokinetic pulses, cold extremities, presence of seizures, blood L-lactate concentration > 6.0 mmol/L, and increased serum potassium and total bilirubin concentrations – predictors of mortality in foals (2025)

The Systemic Inflammatory Response Syndrome and Predictors of Infection and Mortality in 1068 Critically Ill Newborn Foals, P Wilkins et al, 2025



Neonatal Encephalopathy


FOR
DUMMIES

Peripartum Asphyxia Syndrome

Perinatal Maladaptation Syndrome

Hypoxic Ischemic Encephalopathy

Maladjustment Syndrome

Neonatal Encephalopathy

“Dummy Foals”

“Wanderers”

“Barkers”

Neonatal Encephalopathy

- Occurs from hypoxia/ischemia at or around time of parturition
  - Possibly from chronic asphyxia
  - Associated with adverse peripartum events (dystocia, placental separation)
  - Complex cascade of cellular events occurs due to the lack of oxygen to CNS
- May not be associated with abnormal birth or hypoxic episode

Neonatal Encephalopathy - Pathogenesis

1. **Ischemic/hypoxic events** (oxygen/energy depravation)

   Hypoxemia – a decreased amount of oxygen in the blood

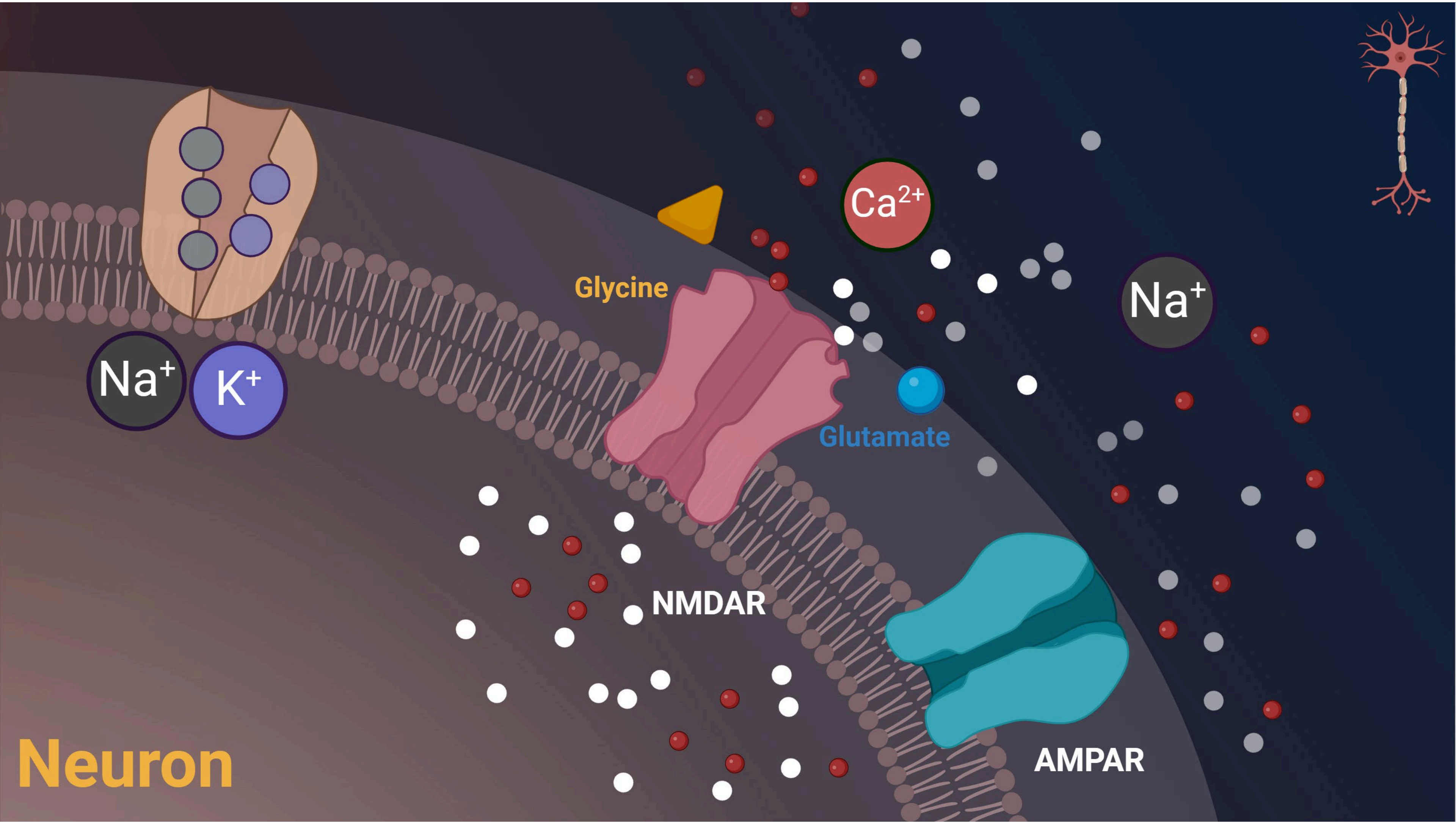
   Ischemia – a decreased rate of blood perfusion of the tissues

2. **Nonischemic events** (endocrine – increased neurosteroids concentration)

Neonatal Encephalopathy

- Hypoxia and Ischemia affect entire body:
  - Central nervous system,
  - Gastrointestinal tract (necrotizing enterocolitis)
  - Kidneys (renal failure)

  These organs are particularly sensitive to oxygen deprivation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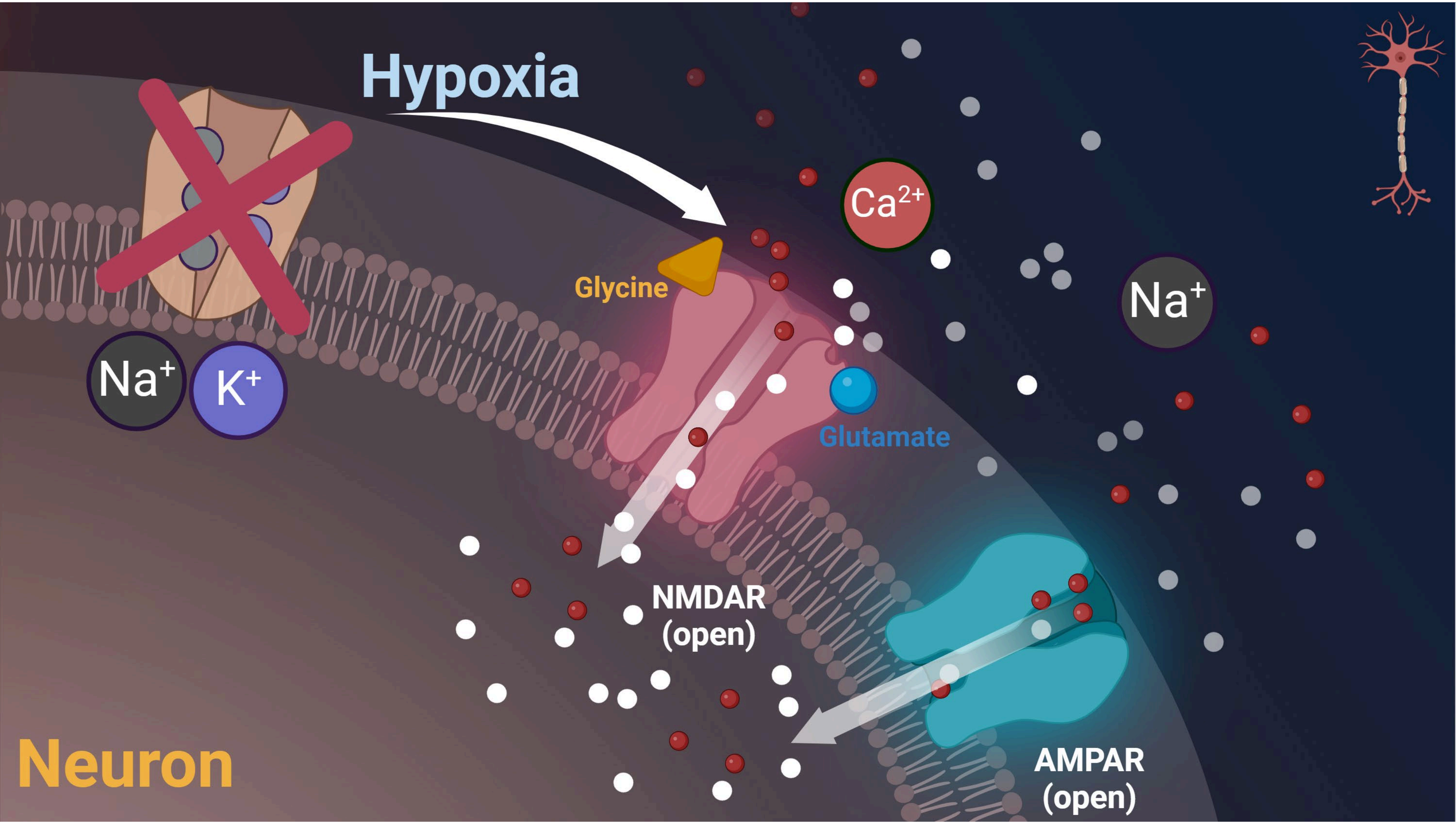
Glutamate
NMDAR
AMPAR
Neuron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NMDAR
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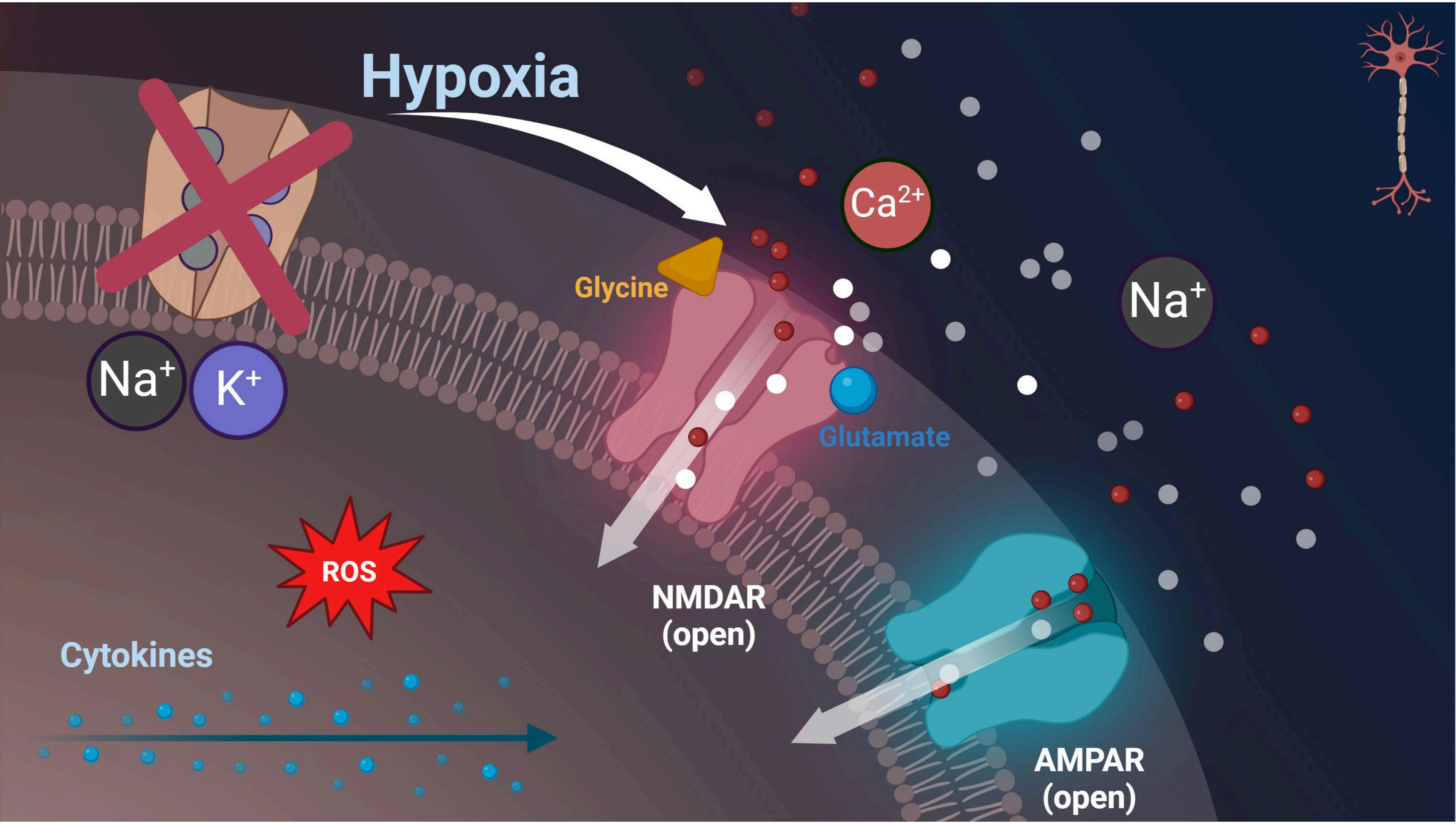
AMPAR
(open)
Neuron


Hypoxia
Glycine
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Glutamate
ROS
NMDAR (open)
Cytokines
AMPAR (open)

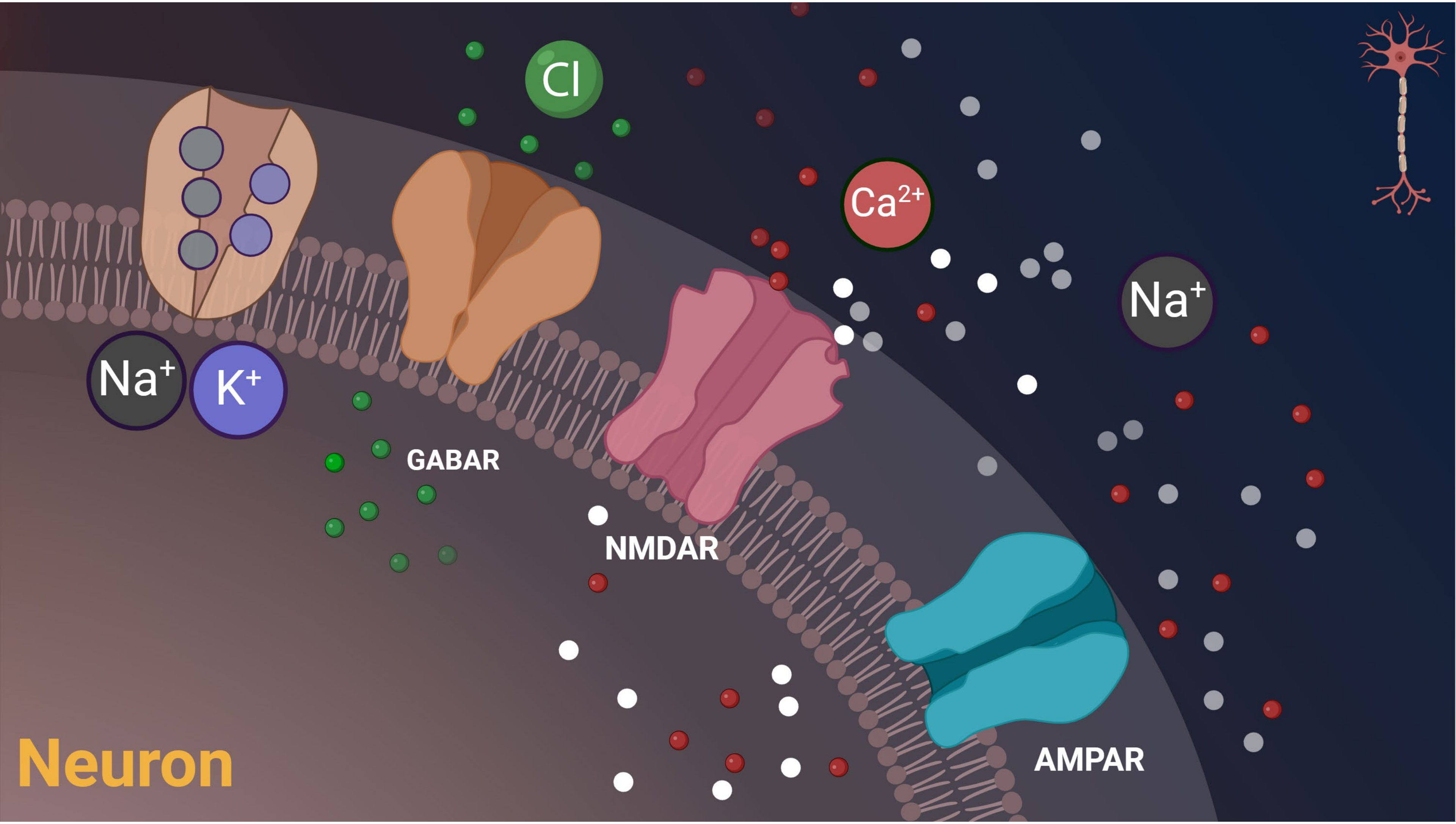
Neonatal Encephalopathy

- Factors that contribute to HIE
  - Primary Neuronal Damage
    - Lack of oxygen = anaerobic metabolism; decreased ATP
      - Cellular dysfunction of ion pumps
        - Cell swelling
      - Increased Intracellular Ca^{++}
        - Activation of various pathways
  - Secondary Neuronal Damage
    - Free Radical Formation

Neonatal Encephalopathy

- **Increased inflammatory cytokines in CNS** → altered neuronal and microglial function resulting in brain injury and cytotoxic edema

- Altered **neuroactive steroid** concentrations → fetal and neonatal somnolence

Cl
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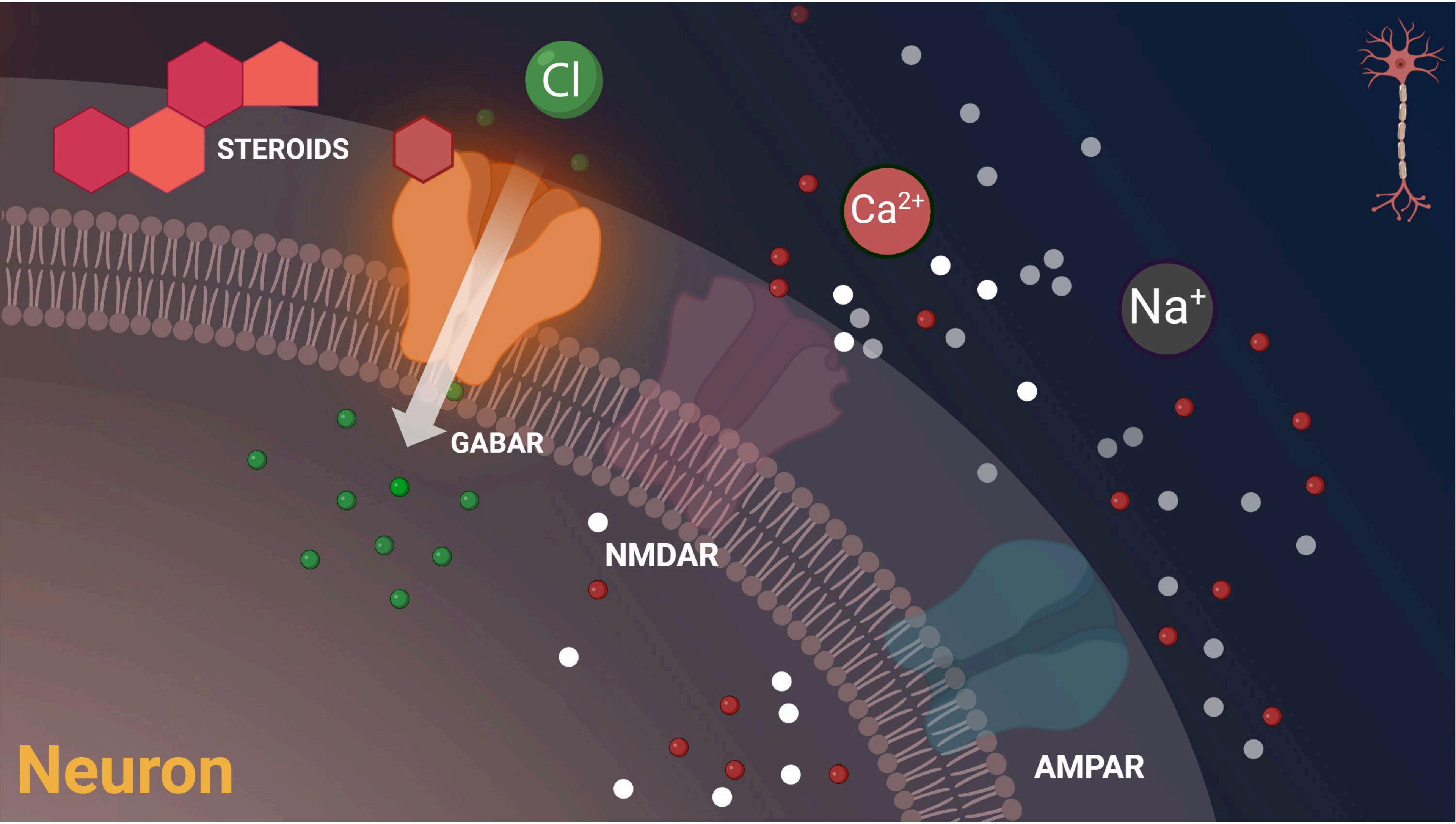STEROIDS
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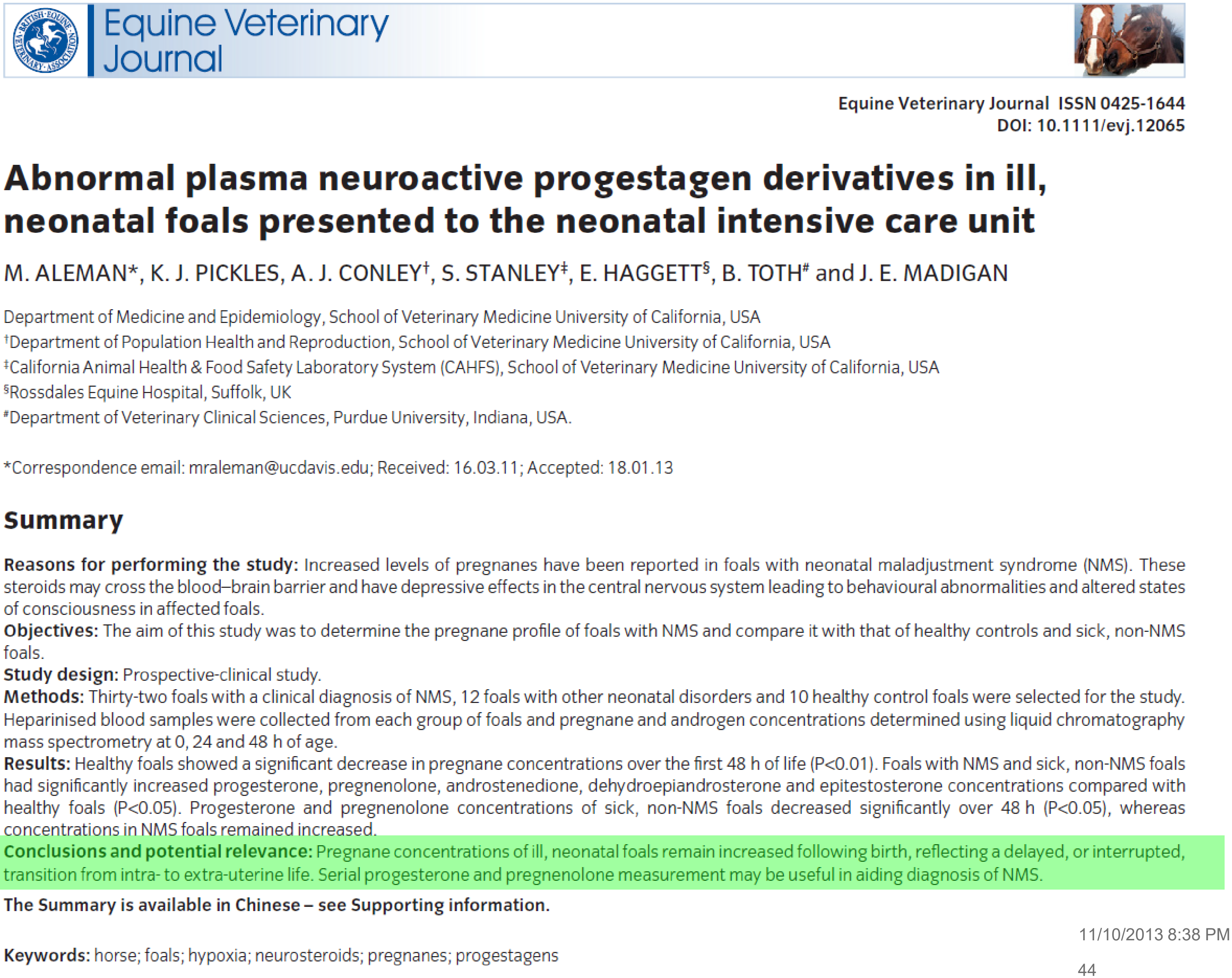
Neuron



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Abnormal plasma neuroactive progestagen derivatives in ill, neonatal foals presented to the neonatal intensive care unit

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Summary

Reasons for performing the study: Increased levels of pregnanes have been reported in foals with neonatal maladjustment syndrome (NMS). These steroids may cross the blood–brain barrier and have depressive effects in the central nervous system leading to behavioural abnormalities and altered states of consciousness in affected foals.
Objectives: The aim of this study was to determine the pregnane profile of foals with NMS and compare it with that of healthy controls and sick, non-NMS foals.
Study design: Prospective-clinical study.
Methods: Thirty-two foals with a clinical diagnosis of NMS, 12 foals with other neonatal disorders and 10 healthy control foals were selected for the study. Heparinised blood samples were collected from each group of foals and pregnane and androgen concentrations determined using liquid chromatography mass spectrometry at 0, 24 and 48 h of age.
Results: Healthy foals showed a significant decrease in pregnane concentrations over the first 48 h of life ($P<0.01$). Foals with NMS and sick, non-NMS foals had significantly increased progesterone, pregnenolone, androstenedione, dehydroepiandrosterone and epitestosterone concentrations compared with healthy foals ($P<0.05$). Progesterone and pregnenolone concentrations of sick, non-NMS foals decreased significantly over 48 h ($P<0.05$), whereas concentrations in NMS foals remained increased.
Conclusions and potential relevance: Pregnane concentrations of ill, neonatal foals remain increased following birth, reflecting a delayed, or interrupted, transition from intra- to extra-uterine life. Serial progesterone and pregnenolone measurement may be useful in aiding diagnosis of NMS.

The Summary is available in Chinese – see Supporting information.

Keywords: horse; foals; hypoxia; neurosteroids; pregnanes; progestagens

Andalusian foal
Dr. J. Mendoza, Spain

Neonatal Encephalopathy

- **History:**
  - May be born without complication or may have history of dystocia
  - May appear normal for a period of time (first few hours of life to 24 hours old)
  - Foals can be term and have appropriate size or may be dysmature or premature

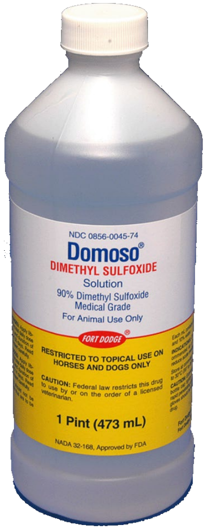
Neonatal Encephalopathy

- **Diagnosis:**
  - History & Signalment

    Premature or dysmature foals
  - No specific clinicopathologic test to definitively diagnose neonatal encephalopathy
  - Diagnosis based on history, clinical signs, ruling out other disease processes, and positive response to supportive treatment

Neonatal Encephalopathy

- **Treatment**
  - Anti-inflammatory & Anti-oxidant drugs
    - Flunixin meglumine
    - Vitamins C & E – anti-oxidants
    - Magnesium
      - Stabilize cell membrane
      - Inhibit free radical production
      - Block NMDA receptors
    - Mannitol – reduces cerebral edema
    - DMSO – free radical scavenger


NDC 0856-0045-74
Domoso®
DIMETHYL SULFOXIDE
Solution
90% Dimethyl Sulfoxide
Medical Grade
For Animal Use Only
FORT DODGE
RESTRICTED TO TOPICAL USE ON HORSES AND DOGS ONLY
1 Pint (473 mL)
NADA 32-168, Approved by FDA

NDC 0517-2610-25
MAGNESIUM SULFATE
INJECTION, USP
50% (0.5 g/mL)
5 grams/10 mL
(4.06 mEq/mL Magnesium)
10 mL SINGLE DOSE VIAL
FOR IM USE
FOR IV USE AFTER DILUTION
Rx Only
AMERICAN REGENT, INC.
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Neonatal Encephalopathy

- **Treatment**
  - Supportive Therapy
    - Nutritional support
    - Fluid therapy
    - Antimicrobial therapy

Neonatal Encephalopathy

Treatment

- Supportive Therapy

  Treatment of FPT (plasma)

  Treatment of seizures

  Oxygen therapy

Keppra® 250 mg
levetiracetam
60 film-coated tablets
ucb

10 mL Multiple-dose
DIAZEPAM
Injection, USP
5 mg/mL
ABBOTT LABORATORIES, NORTH CHICAGO, IL
EXP 1FEB2005 LOT

NDC 10019-027-39
Midazolam HCl Injection
50 mg/10 mL
℞ only
5 mg/mL midazolam (as the hydrochloride)
10 mL Vial
FOR IM OR IV USE
FOR INVENTORY ONLY — APPROXIMATION

1 mL DOSETTE® VIAL
NDC 0641-0477-21
PHENOBARBITAL
SODIUM INJECTION, USP
130 mg/mL
Rx only

NDC 0517-2610-25
MAGNESIUM SULFATE
INJECTION, USP
50% (0.5 g/mL)
5 grams/10 mL
(4.06 mEq/mL Magnesium)
10 mL SINGLE DOSE VIAL
FOR IM USE
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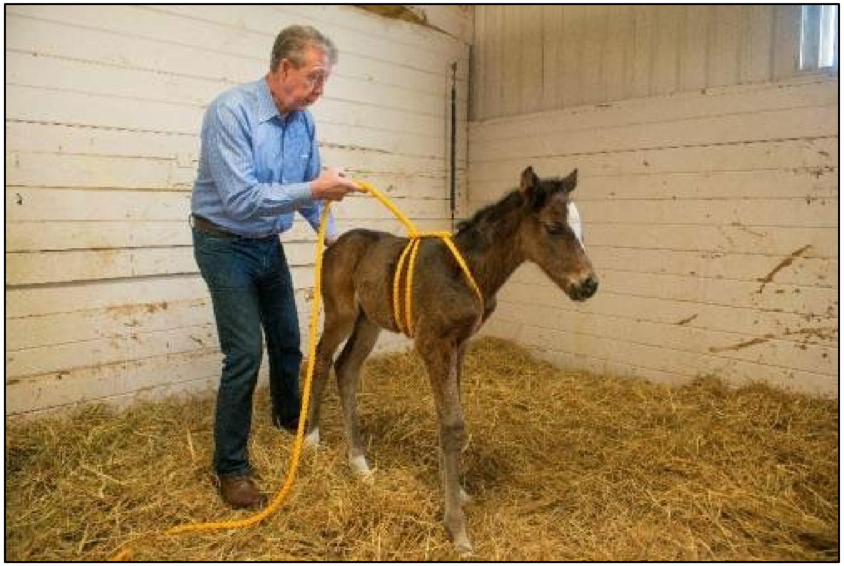
Neonatal Encephalopathy

Treatment

- ✓The “Madigan Squeeze Technique” (MST) - creates pressure that mimics the normal birth canal pressures
  - ✓signal the foal to transition from sleeping in utero to wakefulness



https://www.equineneonatalmanual.com/foalsqueezing

Neonatal Encephalopathy

- **Prognosis:**
  - Many of these foals (~75%) will recover and be normal with adequate supportive therapy.
  - Occasionally, residual neurologic deficits may be noted.

Neonatal Encephalopathy

- Prognosis
    - Mental development index (MDI)?